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(54) Title: CARRIER MATERIAL FOR DRY POWDER INHALATION

(57) Abstract: The present invention relates to a carrier material for use in dry powder inhalation formulations, comprising carrier particles that are spherical in nature and contain no amorphous material. In addition the invention provides a method for the preparation of a carrier material for use in dry powder inhalation formulations, comprising the steps of providing a carrier base material consisting of sperical carrier particles; and crystallising the carrier base material in order to remove amorphous material present in the particles to obtain the carrier material.

CARRIER MATERIAL FOR DRY POWDER INHALATION

The present invention relates to a carrier material for use in dry powder inhalation formulations, to the process for manufacture of these carrier materials and to dry powder inhalation formulations using the carrier materials.

Dry powder inhalers have been in existence since the late 1960's. Interest in this technique for delivering pharmacological active components to the lungs was initially limited due to the popularity of pressurized metered dose inhalers (pMDI's). However, since the decision to eliminate CFC's from pMDI's due to environmental issues, dry powder inhalers are becoming more popular.

Traditionally, formulations for dry powder inhalation comprise a pharmacologically active component and an inert carrier material, being in most cases α-lactose monohydrate crystals. The active component is usually micronised with a particle size less than 5 μm, to enable deposition in the lower levels of the lungs. The purpose of the inert carrier is to aid flow and to prevent the formation of agglomerates of the active component which agglomerates can not be dispersed, thus preventing deposition at the site of action.

It was however found that over time α-lactose does not have an optimal flow, which may lead to problems, such as clogging, in the inhaler. In addition, it was found that α-lactose monohydrate does not always lead to a 100% drug delivery. Ideally, upon inhalation of a dry powder inhalation formulation, the carrier hits the throat, after which the drug, which is in loose association with the carrier, detaches therefrom and is transported to the lungs where it has its effect. In case the drug does not end up in the right location, i.e. the lung, there may arise problems for the patient.

Due to the increased interest in dry powder inhalation formulations, other concepts have been

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investigated include the use of anhydrous ß-lactose as a carrier or agglomerates of the active component without carrier. These concepts have not led to satisfactory results either.

It is therefore the object of the present invention to provide an improved carrier material for dry powder inhalation formulations.

In the research that led to the present invention it was found that spray-dried carrier material consists of spherical particles, which show excellent flow characteristics, but that spray dried products may contain amorphous material which can undergo crystallisation in the presence of moisture. When this crystallisation occurs in the presence of the active ingredient, such as a drug, it may become bound and will not detach upon inhalation. The presence of amorphous material can therefore potentially affect stability and performance of the inhalation formulation, if moisture uptake occurs within the dry powder inhaler. It was found that in order to improve the functionality of spray dried products in dry powder inhalation formulations a crystallisation step should be incorporated into the manufacture of the carrier material. The purpose of the crystallisation step is to remove substantially all, and preferably all the amorphous material present.

The present invention thus relates to a carrier material, comprising carrier particles that are spherical in nature and contain substantially no or no amorphous material.

Such carrier material is for example obtainable by a method comprising the steps of:

a) providing a carrier base material consisting of spherical carrier particles; and

b) crystallising the carrier base material in order to remove amorphous material present in the particles to obtain the carrier material.

The provision of the spherical carrier base material can be achieved by spray drying a starting

material to obtain a powder that consists of substantially spherical particles of the carrier material that still contain amorphous material. A suitable method for obtaining such carrier base material is described in EP-239 172, which is incorporated herein by reference. In summary, the method described therein comprises feeding a slurry of crystalline α-lactose hydrate in a saturated lactose solution to a spray drier and drying the same, wherein the selection of the ratio between the amounts of crystalline material and dissolved lactose in the slurry determines the ratio between the amounts of crystalline and amorphous lactose in the spray dried product. The person skilled in the art of spray drying can modify the process conditions to obtain a suitable spray dried product based on his common general knowledge of spray drying.

The present invention thus provides a spray dried product with substantially no or no amorphous material, by virtue of which it has excellent flow properties and is stable with regard to air moisture.

Preferred carrier materials are those known to be useful for dry powder inhalation formulations. In particular these are monosaccharides such as glucose, fructose, mannose etc. and the polyols derived therefrom like sorbitol, mannitol etc. , disaccharides such as lactose, maltose, sucrose and their derivatives such as lactitol, maltitol, and oligo- and polysaccharides such as dextrins and starches.

The carrier base material for the spray drying process can be one of the above mentioned materials or combinations of these. Preferably, the carrier base material is a crystalline carrier base material, in particular a crystalline sugar such as glucose, fructose, sucrose or mannitol and most preferably the carrier base material is lactose.

The amorphous content of the spray dried product (base powder) is generally within the range 0.5% to 50%. The amorphous material present in the spray dried

powder particles can then be crystallised by any suitable method. A particularly preferred method yielding good results is the use of a fluid bed dryer using suitable conditions with regard to temperature and relative humidity which allow the amorphous material to crystallise. Suitable temperature conditions are a temperature of 20 to 100°C, preferably 30 to 90°C, more preferably 40 to 80°C, even more preferably 50 to 70°C, most preferably 60°C in combination with a suitable relative humidity of 80% to 10%, preferably 70 to 15%, more preferably 60 to 20%, even more preferably 50 to 25%, further more preferably 40 to 30%, most preferably 35%.

The carrier material of the invention produced for the purpose of dry powder inhalation has a particle size typically between 1 μm and 400 μm. Preferably, the particle size is between 40 μm and 300 μm. Typically, at least 90% of the particles are within this latter range.

The present invention furthermore relates to a dry powder inhalation formulation which contains a carrier material of the invention and at least one pharmacologically active component. The active component may be selected from the group consisting of steroids, sympathomimetics, mucolytics, proteins, peptides, sodium cromoglycate or from the group consisting of hypnotics, sedatives, analgesics, ani-inflammatory agents, anti-histamines, anticonvulscents, muscle relaxants, anti-spasmodics, anti-bacterials, antibiotics, cardiovascular agents and hypoglycaemic agents.

Preferably the active component is budesonide or alternatively sodium cromoglycate.

The performance of carrier material of the present invention is demonstrated in the following examples that are given for illustration purposes only.

EXAMPLES

EXAMPLE 1

Comparison to α-lactose monohydrate

α-Lactose monohydrate is commonly used in dry powder inhalation formulations. It has generally a good performance, but over time the problems described in the specification, i.e. crystallisation upon contact with air humidity and thus decreased stability and performance, may occur.

To demonstrate the performance of the invention in comparison to α-lactose monohydrate (standard crystal form of lactose), non-pretreated α-lactose monohydrate and a selected size fraction of the carrier material of the invention were used in an inhalation formulation. As a second control standard spray dried lactose was used.

A suspension of a fine milled α-lactose monohydrate powder in an aqueous lactose solution was spray dried, resulting in a spray dried powder with approximately 20% amorphous lactose. This represents the standard spray dried lactose.

To prepare the carrier material of the invention, the amorphous lactose in the spray dried powder obtained above was then crystallised by a treatment in a fluid bed dryer at a temperature of 60°C and a relative humidity of 35 % to obtain a powder having 90% of the particles in the particle size range from 40-300 μm.

α-Lactose monohydrate was obtained from DMV International, Veghel, the Netherlands.

Budesonide was used as the active component, with an active ingredient to carrier ratio of 1:62.5. The formulations were prepared using a tumble mixer. The budesonide concentrations were determined by UV spectroscopy.

The performance of the formulations was assessed in vitro using the multi-stage liquid impinger, with the method described in the USP24. The device used was a multidose inhaler, utilising a reservoir system.

The results obtained are shown in table 1 as a percentage (%) of the nominal dose. The fraction "Stage 3 + 4 + filter" is considered as the fraction reaching the lungs.

Table 1

	% deposition of budesonide		
	-lactose monohydrate	carrier of the invention	standard spray dried lactose
inhaler	19.2	7.6	9.1
throat	14.4	26.0	33.5
stage 1	34.2	37.0	44.1
stage 2	3.1	3.5	3.7
stage 3+4+filter	30.7	29.6	15.0
total recovered	101.6	104.7	105.4

EXAMPLE 2

Comparison between carrier material of the invention and standard spray dried material

Analogous to the method described in Example 1, two inhalation preparations of sodium cromoglycate using carrier material of the invention and standard spray dried material were prepared and tested. Table 2 shows the results.

Table 2

	% deposition of cromoglycate	
	carrier of the invention	standard spray dried material
inhaler	6.1	4.2
throat	26.0	21.0

stage 1	39.9	50.5
stage 2	7.5	8.9
stage 3+4+filter	17.1	13.6
total recovered	96.4	98.3

EXAMPLE 3

Comparison between carrier material of the invention and standard spray dried material

Two inhalation preparations of budesonide were prepared using carrier material of the invention and standard spray dried material, wherein the carrier material of the invention was prepared at varying spray drying conditions. The preparation and testing of these formulations was as described in Example 1. The deposition values given in Table 3 are the average of two determinations.

Table 3

	% deposition of budesonide			
	40°C/55%RH	60°C/35%RH	74°C/22%RH	standard spray dried lactose
inhaler	8.4	7.6	8.8	9.1
throat	23.8	26.0	27.6	33.5
stage 1	38.4	37.0	37.2	44.1
stage 2	3.7	3.5	3.8	3.7
stage 3+4+filter	28.8	29.6	20.9	15.0
total recovered	103.1	104.7	98.3	105.4

CLAIMS

1. Carrier material for use in dry powder inhalation formulations, comprising carrier particles that are spherical in nature and contain no amorphous material.

2. Method for the preparation of a carrier material for use in dry powder inhalation formulations, comprising the steps of:

a) providing a carrier base material consisting of spherical carrier particles; and

b) crystallising the carrier base material in order to remove amorphous material present in the particles to obtain the carrier material.

3. Method as claimed in claim 2, wherein the provision of the spherical carrier base material is achieved by spray drying a starting material under conditions that lead to a powder that consists of substantially spherical particles of the carrier material that still contain amorphous material.

4. Method as claimed in claim 2 and 3, wherein the spherical carrier base material is produced by feeding a slurry of crystalline α-lactose hydrate in a saturated lactose solution to a spray drier and drying the same.

5. Method as claimed in claims 2-4, wherein step b) is performed at a temperature between 20 and 100°C, preferably between 30 and 90°C, more preferably between 40 and 80°C, even more preferably between 50 and 70°C, most preferably at 60°C in combination with a relative humidity of 80% to 10%, preferably 70 to 15%, more preferably 60 to 20%, even more preferably 50 to 25%, further more preferably 40 to 30%, most preferably 35%.

6. Method according to claims 1-5, wherein the carrier material is produced of a monosaccharide, in particular glucose, fructose, mannose, or of the polyols derived therefrom, in particular sorbitol, mannitol.

7. Method according to claims 1-5, wherein the carrier material is produced of a disaccharide, in particular lactose, maltose, sucrose, or their polyols, in particular lactitol, mannitol.

8. Method according to claims 1-5, wherein the carrier material is produced of oligosaccharides or polysaccharides, in particular dextrins and starches.

9. Method according to claims 1-7, where the material is produced of a crystalline sugar, in particular glucose, fructose, mannitol, or sucrose.

10. Method according to claims 1-7, wherein the material is produced of lactose.

11. Carrier material for use in dry powder inhalation formulations obtainable by a method as claimed in claims 2-10.

12. A carrier material according to claim 11, wherein the particle size of the material is between 1 μm and 400 μm.

13. A carrier material according to claim 12, wherein the particle size of the material is between 40 μm and 300 μm.

14. A dry powder inhalation formulation which contains a carrier material according to claims 1 or 11-13 and at least one pharmacologically active component.

15. A dry powder inhalation formulation according to claim 14, in which the active component is selected from the group consisting of steroids, sympathomimetics, mucolytics, proteins, peptides, sodium cromoglycate.

16. A dry powder inhalation formulation according to claim 14, in which the active component is selected from the group consisting of hypnotics, sedatives, analgesics, ani-inflammatory agents, anti-histamines, anticonvulscents, muscle relaxants, anti-spasmodics, anti-bacterials, antibiotics, cardiovascular agents and hypoglycaemic agents.

17. A dry powder inhalation formulation according to claim 14, wherein the active component is budesonide.

18. A dry powder inhalation formulation according to claim 14, wherein the active component is sodium cromoglycate.

INTERNATIONAL SEARCH REPORT

Int[redacted]ial Application No
[redacted]EP 01/08395

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K47/26 A61K31/58 A61K31/35 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 239 172 A (DMV CAMPINA BV) 30 September 1987 (1987-09-30) citéd in the application abstract examples 1-3 claims 1-6 ---	2-18
X	US 5 376 386 A (GANDERTON DAVID ET AL) 27 December 1994 (1994-12-27) abstract column 1, line 7 -column 4, line 68 examples 1-7 claims 1-7 --- -/--	2-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inte al Application No
EP 01/08395

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 5 874 063 A (TROFAST EVA ET AL) 23 February 1999 (1999-02-23) abstract column 1, line 11 -column 4, line 56 examples 1-12 claims 1-20	2-18
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1

Present claim 1 relates to a product defined by reference to a desirable characteristic or property, namely

the carrier particles are spherical in nature;
the carrier particles contain no amorphous material.

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Art. 6 PCT and/or disclosure within the meaning of Art. 5 PCT for only a very limited number of such products, namely one specific method for the preparation of a lactose-based carrier material. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Art. 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely the subject-matter of claims 2-18 (excluding any dependencies on claim 1).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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Inter[redacted] Application No
P[redacted]P 01/08395

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